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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/686,880	10/12/2000	Austin G. Smith	06999.0009	5994

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	25

DATE MAILED: 08/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

Applicants' amendments filed 5-15-03 and 6-23-03 have been entered. Claims 42, 44-49, 54 and 65 have been amended. Claim 53 has been canceled. Claims 66-78 have been added. Claims 42, 44-51, 54, 58 and 64-78 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 78 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendments filed 5-15-03 and 6-23-03 necessitate this new ground of rejection.

The phrase "neural progenitors" in the newly added claim 78 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "neural progenitors". It is unclear whether neural progenitor cells or neural progenitor specific genes or others are intended.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Office Action Summary	Application No.	Applicant(s)	
	09/686,880	SMITH ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5-15-03 and 6-6-23-03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,44-51,54,58 and 64-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,44-51,54,58 and 64-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

3. Claims 42, 44-51, 54, 58 and 64-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendments filed 5-15-03 and 6-23-03 necessitate this new ground of rejection.

Claim 42 has been amended to read on a method for generating a culture of purified or enriched neural progenitor cells by introducing into a pluripotent cells a selectable marker that is differentially expressed in neural progenitor cells compared with its expression in other cells, wherein **expression of the selectable marker is operatively linked to expression of a SOX gene**. The newly added claim 66 reads on a method for generating a culture of purified or enriched neural progenitor cells by introducing into a pluripotent cells a selectable marker that is differentially expressed in neural progenitor cells compared with its expression in other cells, wherein **expression of the selectable marker is operatively linked to expression of a gene that is differentially expressed in neural progenitor cells**.

The phrases "wherein expression of the selectable marker is operatively linked to expression of a SOX gene" and "expression of the selectable marker is operatively linked to expression of a gene that is differentially expressed in neural progenitor cells" are considered new matter. The specification only discloses "introducing into a multipotential cell a selectable marker that is differentially expressed in cells of the selected linage compared with its expression in other cells" and a construct containing a beta-galactosidase gene under the control of a SOX2 promoter. The claims encompass linking expression of the selectable marker to not only SOX

gene but also downstream genes that are under the control of SOX gene expression or downstream genes that are under the control of genes that are differentially expressed in neural progenitor cells. The specification fails to provide sufficient description to support expression of a selectable marker operatively linked to expression of a SOX gene or a gene that is differentially expressed in neural progenitor cells. Claims 44-51, 54, 58, 64 and 65 depend on claim 42 and claims 67-78 depend on claim 66 but fail to obliterate the new matter rejection.

4. Claims 42, 44-51, 54, 58 and 64-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating a neural progenitor cell culture by integrating selectable marker gene, such as neo, into Sox gene that is induced by retinoic acid and said marker gene is under the control of Sox gene promoter, does not reasonably provide enablement for a method for generating a neural progenitor cell culture by introducing into a pluripotent cell a selectable marker and/or a second selectable marker that is differentially expressed in neural progenitor cells, wherein expression of the selectable marker is operatively linked to expression of a SOX gene or expression of the selectable marker is operatively linked to expression of a gene that is differentially expressed in neural progenitor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants' amendments filed 5-15-03 and 6-23-03 necessitate this new ground of rejection.

Claim 42 has been amended to read on a method for generating a culture of purified or enriched neural progenitor cells by introducing into a pluripotent cells a selectable marker that is

differentially expressed in neural progenitor cells compared with its expression in other cells, wherein **expression of the selectable marker is operatively linked to expression of a SOX gene**. The newly added claim 66 reads on a method for generating a culture of purified or enriched neural progenitor cells by introducing into a pluripotent cells a selectable marker that is differentially expressed in neural progenitor cells compared with its expression in other cells, wherein **expression of the selectable marker is operatively linked to expression of a gene that is differentially expressed in neural progenitor cells**.

The claims encompass using any selectable marker that its expression is operatively linked **to expression** of a SOX gene or operatively linked to **expression** of a gene that is differentially expressed in neural progenitor cells. The claims encompass linking expression of the selectable marker to not only SOX gene but also downstream genes that are under the control of SOX gene expression or downstream genes that are under the control of genes that are differentially expressed in neural progenitor cells. The specification discloses generating a neural progenitor cell culture by inducing ES cells differentiation with retinoid acid and integrating selectable marker gene, such as neo, into Sox 2 gene of said pluripotent cells for selection of neural progenitor cells, wherein said marker gene is under the control of Sox 2 gene promoter.

The specification fails to provide adequate guidance and evidence that mere introduction of one or two selectable marker into any pluripotent cells and/or using cells expressing gene other than Sox gene would produce purified neural progenitor cells. The selectable marker has to be integrated into a gene and under the control of the promoter of said gene, or promoter that is specific for neural progenitor cells, that is expressed during the differentiation of the

pluripotent cells to neural progenitor cells because the selectable marker needs to be expressed during the process of differentiating into neural progenitor cells in order to select neural progenitor cells. A neural specific marker gene itself expressed inside the pluripotent cells may be used as a marker for identifying neural progenitor cells but it is insufficient for producing purified and enriched neural progenitor cells because non-neural progenitor cells need to be removed by selection pressure, such as antibiotics.

The specification also fails to provide adequate guidance for the genes whose expressions are under the control of the expression of SOX gene or genes that are differentially expressed in neural progenitor cells and what element is physically operatively linked to the selectable marker gene such that expression of SOX gene, gene that is differentially expressed in neural progenitor cells or its downstream genes can regulate the expression of the selectable marker gene. There is no evidence of record that mere introduction of one or two selectable marker into any pluripotent cells, either via random integration or homologous recombination, wherein expression of the selectable marker is operatively linked to expression of a SOX gene or operatively linked to expression of a gene that is differentially expressed in neural progenitor cells, and/or using cells expressing gene other than Sox gene would produce purified neural progenitor cells. The purification and enrichment of neural progenitor cells during the differentiation of any pluripotent cells to neural progenitor cells require selection pressure that can remove non-neural progenitor cells and such selection pressure needs to be in a neural progenitor cell specific manner. Absent the evidence of the downstream genes of SOX gene or genes that are differentially expressed in neural progenitor cells, one skilled in the art at the time of the

invention would not know how to use the selectable marker for producing purified or enriched neural progenitor cells from pluripotent cells by using those downsteam genes.

The neural specific genes cited in claim 76, e.g. Pax3, MAP2/tau and GFAP, appear to be marker genes for the SOX-selected neural progenitor cells. They appear to be expressed after the neural progenitor cells have been purified and enriched by SOX selection and they don't appear to be expressed during the selection process of the neural progenitor cells from pluripotent cells. The specification fails to provide adequate guidance and evidence whether operatively linked a selectable marker to the promoters of those gene or promoters of their downstream genes would selectively express the selectable marker during the process of differentiation from pluripotent cells to neural progenitor cells so as to purify or enrich neural progenitor cells from a mixture of different cell types. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed invention and would require undue experimentation to practice over the full scope of the invention claimed.

5. Claims 42, 44-51, 54, 58, 64 and 65 remain rejected and claims 66-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating a neural progenitor cell culture by integrating selectable marker gene, such as neo, into Sox gene that is induced by retinoic acid and said marker gene is under the control of Sox gene promoter, does not reasonably provide enablement for a method for generating a neural. progenitor cell culture by introducing into a pluripotent cell a selectable marker and/or a second selectable marker that is differentially expressed in neural progenitor cells, wherein expression of the selectable marker is operatively linked to expression of a SOX gene or expression of the

selectable marker is operatively linked to expression of a gene that is differentially expressed in neural progenitor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants amended claims to specify the selectable marker is operatively linked to a SOX gene and argue that example of the specification discloses using SOX1 and SOX2 genes (amendment, p. 7, 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-12-02 (Paper No. 19) and the reasons set forth above under the new 35 U.S.C. 112 first paragraph rejection.

Applicants argue that the newly added claims 66-78 specify the expression of the selectable marker is operatively linked to expression of a neural progenitor cell-specific gene (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-12-02 (Paper No. 19) and the reasons set forth above under the new 35 U.S.C. 112 first paragraph rejection.

Applicants cite references Lee et al., Morgan & Sargent, Lamb & Harland, Mizuseki et al., Pattyn et al., Morin et al., and Blass-Kampmann et al. and Dr. Meng Li's declaration and argue that there are many genes with expression pattern specific to neural progenitor cells known in the art (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-12-02 (Paper No. 19) and the reasons set forth above under the new 35 U.S.C. 112 first paragraph rejection. Those genes appear to be expressed after the neural progenitor cells have been purified and enriched and those genes appear to be expressed for further differentiation of neural progenitor cells to more specified neural cells. There is no

evidence of record that these genes are expressed during the selection process of the neural progenitor cells from pluripotent cells. The specification fails to provide adequate guidance and evidence whether operatively linked a selectable marker to the promoters of those gene or promoters of their downstream genes would selectively express the selectable marker during the process of differentiation from pluripotent cells to neural progenitor cells so as to purify or enrich neural progenitor cells from a mixture of different cell types.

Applicants argue that selection of a stimulant is not critical for the claimed invention and any stimulant can be used for the invention (amendment, p. 9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-12-02 (Paper No. 19). Different stimulant could stimulate different set of gene expression in pluripotent cells and the specification fails to disclose what genes would be expressed by stimulant other than retinoic acid during the differentiation of any pluripotent cells to neural progenitor cells. Absent the revelation of the genes that would be induced during the differentiation of any pluripotent cells to neural progenitor cells by stimulant other than retinoic acid, one skilled in the art at the time of the invention would not know how to construct a vector expressing the selectable maker under the control of a specific gene promoter for the purification of neural progenitor cells from pluripotent cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.